



Bronchodilator effect of oral doxofylline and procaterol in asthma: A randomized crossover study

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Background



- Inhaled corticosteroids (ICS) is the main treatment for asthma¹
- Oral bronchodilators might be used useful as adjunctive treatment especially in patients, who not achieved controlled asthma or poor inhalation technique¹

Objective



- To compare the bronchodilator effect and asthma symptoms between doxofylline and procaterol in adults with asthma



Methods



- A crossover randomized controlled trial at Thammasat University Hospital, Thailand
- From June 2022 to December 2022
- EC approval at Thammasat University

Methods

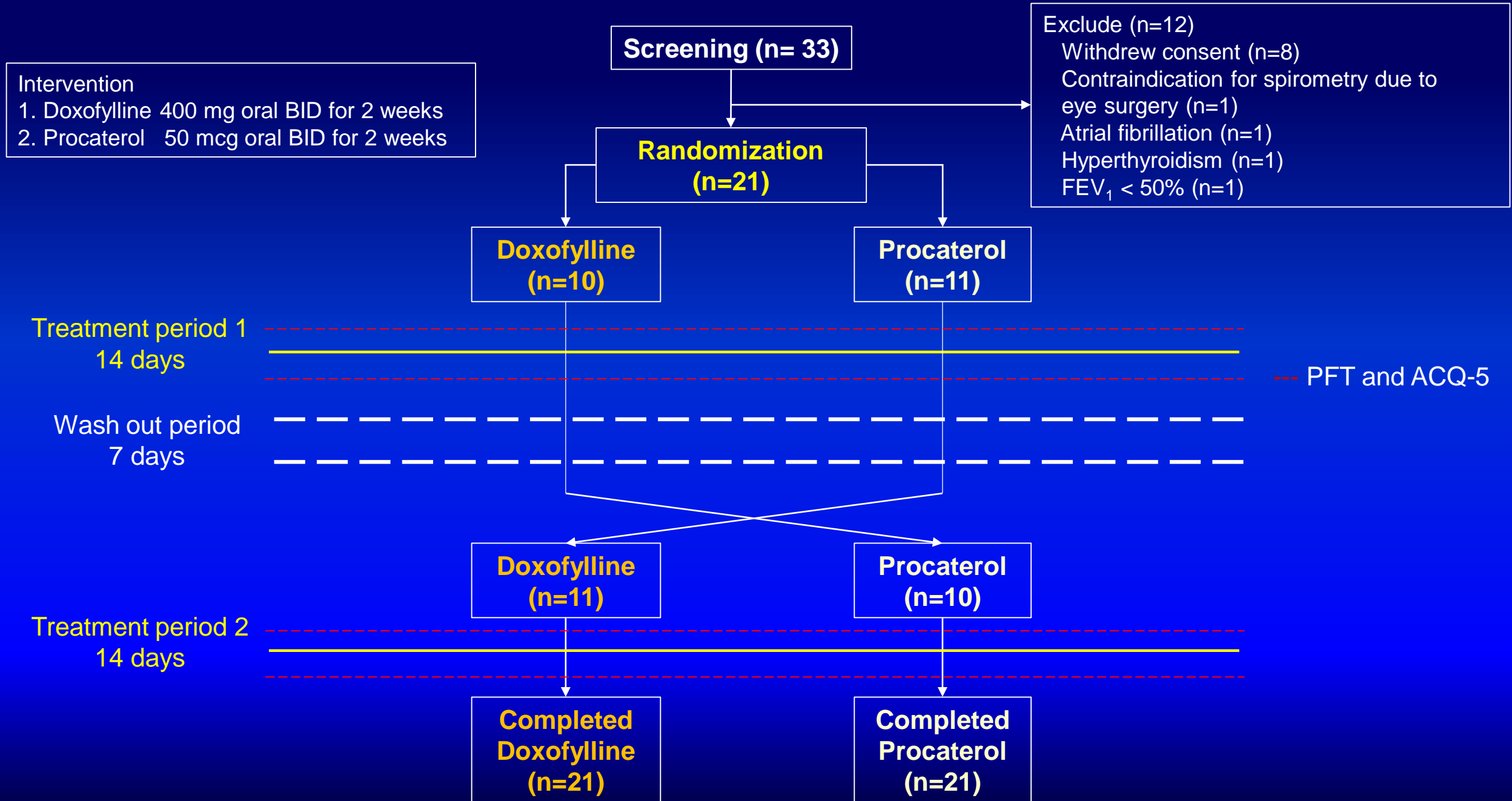


Inclusion criteria

- Asthma diagnosed according to GINA 2022
- Age \geq 18 years
- On ICS/LABA treatment

Exclusion criteria

- Asthma exacerbation within 3 months
- On systemic steroid treatment 3 months
- On biologic treatment
- 10-pack-year smoking history
- Comorbidity eg, AF, chronic heart diseases, chronic cerebrovascular diseases, chronic liver diseases, chronic renal diseases, hyperthyroidism, COPD and other chronic lung diseases
- Pregnancy or lactation
- Inability to perform spirometry
- $FEV_1 < 50\%$ predicted
- Allergic to doxofylline or procaterol



Outcomes



- **Primary outcome:** The difference in spirometry parameters and asthma symptoms between doxofylline and procaterol
- **Secondary outcomes:** The changing before and after treatment in spirometry parameters, ACQ-5 scores, asthma exacerbation and adverse event in each medication

Statistical Analysis



- **Calculated sample size = 18** (90%power, type 1 error of 0.05)
- **Randomization with the block of four**
- Descriptive statistics
 - Categorical data: number (%)
 - Continuous data: mean \pm standard deviations
- Comparative statistics
 - Categorical data: Pearson's Chi-square test or Fischer's exact test
 - Continuous data: Student T-test (independent & paired)
- A two-sided p-value < 0.05 was considered statistically significant

Results



- **21 asthmatic patients** were included from June 2022 to December 2022

Characteristic	Total (n = 21)
Age, years	53.0 ±14.80
Male / female	5 (23.8) / 16 (76.2)
Body mass index, kg/m ²	25.4 ±3.60
Formerly smoking	1 (4.8)
Smoking, pack-years	0.36±1.64
Comorbidity	
Allergic rhinitis	21 (100)
Hypertension	9 (42.9)
Hyperlipidemia	9 (42.9)
Obstructive sleep apnea	2 (9.5)
Medication	
ICS + LABA	20 (95.2)
ICS + LABA + LAMA	1 (4.8)
Daily dose of ICS as budesonide equivalent, mcg/day	560 ±394.36
INS	21 (100)
LRTA	9 (42.9)
Anti-Histamine	14 (66.7)

Data presented as n (%) or mean±SD

Characteristic	Total (n = 21)
Symptom control questionnaire	
ACQ-5, scores	1.38 ±1.10
ACT, scores	23.1 ±0.70
Laboratory data	
Blood eosinophils, %	3.97 ±2.50
Blood eosinophils counts, cells/mm ³	293.5 ±186.10
Spirometry data	
FVC, L	2.81±0.73
FVC, %predicted	102.3±15.60
FEV ₁ , L	2.15±0.62
FEV ₁ , %predicted	93.8 ±12.00
FEV ₁ improvement after BD test, %	4.3±7.50
FEV ₁ /FVC, %	76.9±8.70
PEF, L/s	6.32±1.65
PEF, %predicted	97.3 ±14.00
FEF ₂₅₋₇₅ , L/s	1.82±0.97
FEF ₂₅₋₇₅ , %predicted	62.7±21.70

Study outcomes

	Doxofylline (n=21)	Procaterol (n=21)	P-value
Spirometry data change from baseline			
FVC, L	-0.190±0.157	0.002±0.155	0.659
FVC, %predicted	-0.923±6.481	-0.061±6.134	0.660
FVC improvement after BD test, %	0.257±5.294	0.310±7.060	0.978
FEV ₁ , L	0.004±0.177	0.006±0.109	0.967
FEV ₁ , %predicted	0.330±8.449	-0.129±5.093	0.832
FEV ₁ improvement after BD test, %	0.152±6.748	1.152±6.953	0.639
FEV ₁ /FVC, %	0.981±4.336	0.038±3.197	0.427
PEF, L/s	-0.653±11.447	-0.002±0.697	0.781
PEF, %predicted	-0.653±11.447	-0.479±11.246	0.961
FEF ₂₅₋₇₅ , L/s	0.681±12.24	-1.160±12.891	1.000
FEF ₂₅₋₇₅ , %predicted	2.624±26.009	4.143±23.265	0.638
FEF ₂₅₋₇₅ improvement after BD test, %	2.624±26.009	4.143±23.265	0.843
Symptom control score			
ACQ-5, scores	-0.381±0.740	-0.476±0.873	0.705

**No exacerbation
in both groups**

Data	Doxofylline				Procaterol			
	Before	After	Mean change (95% CI)	P-value	Before	After	Mean change (95% CI)	P-value
FVC, L	2.775±0.735	2.756±0.784	-0.190±0.157 (-0.090, 0.052)	0.584	2.768±0.733	2.771±0.762	0.002±0.155 (-0.068, 0.073)	0.945
FVC, %predicted	100.977±16.333	100.054±18.797	-0.923±6.481 (-3.873, 2.027)	0.521	100.485±14.883	100.425±16.576	-0.061±6.134 (-2.853, 2.731)	0.964
FVC improvement after BD test, %	0.295±3.262	0.552±3.337	0.257±5.294 (-2.153, 2.667)	0.826	0.838±4.357	1.148±7.254	0.310±7.060 (-2.904, 3.523)	0.843
FEV ₁ , L	2.131±0.617	2.135±0.619	0.004±0.177 (0.076, 0.085)	0.913	2.158±0.613	2.164±0.662	0.006±0.109 (-0.436, 0.056)	0.798
FEV ₁ , %predicted	92.819±12.331	93.149±13.542	0.330±8.449 (-3.515, 4.16)	0.860	93.983±11.860	93.854±13.782	-0.129±5.093 (-2.448, 2.189)	0.909
FEV ₁ improvement after BD test, %	4.291±7.514	4.443±3.531	0.152±6.748 (-2.919, 3.223)	0.919	3.501±4.971	4.662±9.869	1.152±6.953 (-2.012, 4.317)	0.456
FEV ₁ /FVC, %	77.009±9.356	77.990±8.716	0.981±4.336 (-0.992, 2.955)	0.312	78.148±8.095	78.186±9.078	0.038±3.197 (-1.417, 1.493)	0.957
PEF, L/s	98.196±15.515	97.542±15.839	-0.653±11.447 (-5.864, 4.557)	0.796	96.608±13.330	96.129±16.930	-0.028±0.697 (-0.320, 0.315)	0.988
FEF ₂₅₋₇₅ , L/s	1.870±1.048	1.879±1.007	0.009±0.339 (-0.146, 0.163)	0.909	1.887±0.944	1.895±1.051	0.009±0.320 (-0.137, 0.154)	0.903
FEF ₂₅₋₇₅ , %predicted	64.328±24.286	65.009±22.630	0.681±12.24 (-4.893, 6.253)	0.802	64.765±20.680	63.605±25.261	-1.160±12.891 (-7.028, 4.708)	0.684
FEF ₂₅₋₇₅ improvement after BD test, %	17.471±22.589	20.095±16.685	2.624±26.009 (-9.216, 14.463)	0.649	14.510±16.480	18.65±29.678	4.143±23.265 (-6.447, 14.733)	0.424

Results: Asthma symptoms by ACQ-5



Results: Adverse events



Adverse event	Doxofylline (n=21)	Procaterol (n=21)
Dizziness	1 (4.8)	0
Headache	1 (4.8)	0
Insomnia	1 (4.8)	0
Palpitation	0	8 (38.1)

Data presented as n (%)

Discussion (1)



- This study is the **first** crossover RCT of comparison between two oral bronchodilators in asthma
- No differences in pulmonary functions, asthma symptom and exacerbation between doxofylline and procaterol for asthma treatment
- Both doxofylline and procaterol can improve asthma symptoms although pulmonary functions are previously normal

Discussion (2)



- A RCT study of Goldstein MF et al. showed that **doxofylline** was an effective treatment for relieving airway obstruction with better safety than theophylline¹
- A meta-analysis of Calzetta L et al. showed that both **doxofylline** and theophylline significantly increased FEV₁, reduced the rate of asthma events and use of salbutamol to relieve asthma symptoms compared to placebo. However, theophylline 250 mg had significantly higher risk of AEs than placebo²

1. Goldstein MF, et al. Med Sci Monit 2002;8:CR297-304.

2. Calzetta L, et al. Pulm Pharmacol Ther 2018;53:20-26.

Discussion (3)



- A study of Crowe MJ et al. reported that **procaterol** and salbutamol were clinically similar in increase in FEV₁ in 24 asthmatic patients¹
- A study in 20 asthmatic patients by Tukiainen H et al. showed that **procaterol** was more potent bronchodilator effect of increasing PEF than salbutamol but there was more palpitation than placebo²
- **Our study** showed that both oral doxofylline and procaterol reduced asthma symptoms without serious adverse side effect during treatment

1. Crowe MJ, Br J Clin Pharmacol 1985;19:787-91.

2. Tukiainen H, et al. Curr Med Res Opin 1988;11:236-41.

Discussion (5)



- All step of treatment asthma in GINA 2022 guideline had no oral bronchodilator in recommendation regimens but low dose sustained-release **theophylline** can use add on therapy (Evidence B)¹
- And guideline for adult asthma management in Thailand 2022 by Thai Asthma Council (TAC)² recommended **oral xanthine** as add-on therapy in last step of treatment
- The Guideline for adult asthma management in Thailand by thoracic society of Thailand under royal patronage (TST) 2023³ additional oral **sustained-release theophylline** in 4th step of all 5 steps of treatment after received moderate to high dose of ICS

1. GINA 2022

2. Guideline for adult asthma management in Thailand by TAC 2022

3. Guideline for adult asthma management in Thailand 2023 by TST

Strength & Limitation



This study is the **first** crossover RCT of comparison between two oral bronchodilators for asthma treatment

Study patients had **previously well** controlled symptoms and normal lung functions, so **no differences** were shown between both oral bronchodilators

Conclusion



- **Oral doxofylline and procaterol can significantly improve asthma symptoms, though they are not able to enhance lung functions**

Clinical application



- **Either doxofylline or procaterol may be used as add-on treatment for asthma with uncontrolled symptoms, although there is normal lung functions**



THANK YOU & QUESTION?



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Acknowledgement



- All participants
- All chest staffs of Division of Pulmonary and Critical Care Medicine, Thammasat University
- Medical Diagnostics Unit, Thammasat University Hospital
- Center of Excellence for Allergy, Asthma and Pulmonary Diseases (TU-CAAP), Thammasat University Hospital
- Funding of Faculty of Medicine, Thammasat University

Conflict of Interest



- The authors declare that no conflict of interest
- No funding from pharmaceutical companies